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Does the timing of inhaled dornase alfa matter? ☆

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Abstract

In CF patients with mild or moderate lung disease, the most sensitive spirometric measure of response to dornase alfa is peripheral airflow. Cross-over studies in patients, already stabilised on dornase alfa, indicate that peripheral airflow shows greater improvement when it is administered 30 minutes before airway clearance therapy (ACT) rather than shortly after ACT. These results are consistent with the hypothesis that the major role of dornase alfa is to facilitate expectoration of sputum during ACT. When ACT is performed in the morning, efficacy and safety are similar when dornase alfa is inhaled before bedtime or upon awakening. Most patients may therefore choose the most convenient time of day to inhale dornase alfa provided that they wait at least 30 minutes before performing ACT. Further research is necessary to establish the optimum regimen in patients with more advanced lung disease.

Keywords: Airway clearance therapy; Children; Cystic fibrosis; Pulmozyme; rhDNase; Timing

1. Introduction

Airway clearance is central to the treatment of cystic fibrosis (CF) and is implemented using airway clearance therapy (ACT) and/or exercise together with nebulised dornase alfa. However, the timing of dornase alfa inhalation with respect to ACT that achieves the optimal result has only recently been studied. In clinical practice, the same proportion of patients is reported to inhale it before versus after ACT [1]. There are theoretical grounds to suppose that either regimen might be more beneficial: on the one hand dornase alfa may help patients expectorate sputum more efficiently during subsequent ACT; alternatively dornase alfa inhaled after ACT may be deposited more efficiently into the peripheral airways and thereby promote expectoration of sputum that was not expelled during prior ACT. The purpose of this presentation is to summarise current knowledge on the optimal timing of dornase alfa with respect to ACT.

Dornase alfa reduces the viscoelasticity of CF sputum by cleaving long-chain DNA, a highly viscous macromolecule released by neutrophils during inflammation of the CF airway [2]. *In vitro*, the maximal effects of dornase alfa on CF sputum viscosity and pourability require about 30 minutes [3]. Maintenance therapy with dornase alfa has been shown to improve pulmonary function [4–6] and to reduce the risk of acute pulmonary exacerbations [5,6] as well as antibiotic use and hospitalisation rates [5]. In patients with early lung disease its largest and most sustained effect is on peripheral airflow [6].

A previous study in 52 children with mild-to-moderate CF lung disease who were not on dornase alfa maintenance therapy did not detect any difference in lung function when dornase alfa was initiated 30 minutes before versus 30 minutes after ACT for 2 weeks. However, a post-hoc subanalysis suggested that dornase alfa may be more effective on forced expiratory volume in 1 second (FEV_1) in children chronically colonised with *Ps. aeruginosa* when administered after ACT [7]. The objective of the current research was to determine, in patients already stabilised on dornase alfa treatment, (A) the regimen of timing of dornase alfa with respect to ACT that yields the greatest improvement in peripheral

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flow; and (B) whether it is safe and effective to permit a night's sleep to intervene between dornase alfa inhalation and ACT.

2. Methods

A: Dornase alfa before versus after ACT

CF patients over 5 years of age were eligible for this study if they were able to perform reproducible spirometry, performed daily ACT, and had been on dornase alfa therapy and clinically stable for ≥1 month [8]. Patients were randomised to inhale either placebo 30 minutes before and dornase alfa immediately after ACT, or dornase alfa 30 minutes before and placebo immediately after ACT, in a double-blind, double-dummy fashion. After 3 weeks of treatment they were crossed over to the alternative regimen. All patients continued to perform ACT in the same way as before the intervention and spirometry was measured at home by the investigator. Primary endpoints were peripheral flow as assessed by expiratory flow at 25% of vital capacity (FEF_{75}) after 2 and 3 weeks of each regimen. Secondary endpoints were other spirometric parameters, as well as sputum amount and viscosity and cough frequency, as recorded in a patient diary during the third week of each treatment regimen.

B: Dornase alfa before versus after sleep

Design and inclusion criteria were similar to the previous study [9]. Patients were randomised to inhale either dornase alfa before bedtime and placebo upon awakening, or placebo before bedtime and dornase alfa upon awakening. In both arms of the study, ACT was performed 30 minutes after the morning nebulisation. After 2 weeks of treatment patients were crossed over to the alternative regimen. The primary endpoint was FEF_{75} after 2 weeks of treatment. Secondary endpoints were other pulmonary function tests, cough frequency as assessed by an audio recording of overnight cough sounds and a day- and night-time cough symptom score, oxygen saturation as measured by overnight pulse oximetry, and signs and symptoms as recorded in a patient diary.

3. Results

A: Dornase alfa before versus after ACT

Twenty-five patients were enrolled and 24 completed the study. Mean age was 12 years and, while FEV_1 and FVC were within the normal range at baseline, peripheral flows as assessed by FEF_{75} and forced expiratory flow at 25–75% of vital capacity ($FEF_{25–75}$) were substantially reduced. The treatment groups were well matched (Table 1). The principal ACT techniques used were PEP mask (75%) and the flutter device (13%).

The primary endpoint (FEF_{75}) was significantly higher, by about 6% predicted, after 3 weeks' treatment when dornase alfa was administered 30 minutes before versus immediately after ACT (Fig. 1, Table 2). Neither the difference in FEF_{75} after 2 weeks' treatment nor any of the secondary endpoints was significantly different between the groups.

Table 1
Characteristics of the population in the study of dornase alfa before versus after ACT at baseline for groups 1 and 2 (numbers of patients, or mean with SD) [8]. Reproduced with permission

	Group 1	Group 2	
N	11	13	NS
Sex (male/female)	6/5	7/6	NS
Age (years)	11 (3)	12 (4)	NS
FVC (% predicted)	93 (14)	93 (11)	NS
FEV_1 (% predicted)	88 (16)	88 (11)	NS
FEF_{75} (% predicted)	56 (27)	57 (25)	NS
Use of TOBI (*n*)	7	6	NS

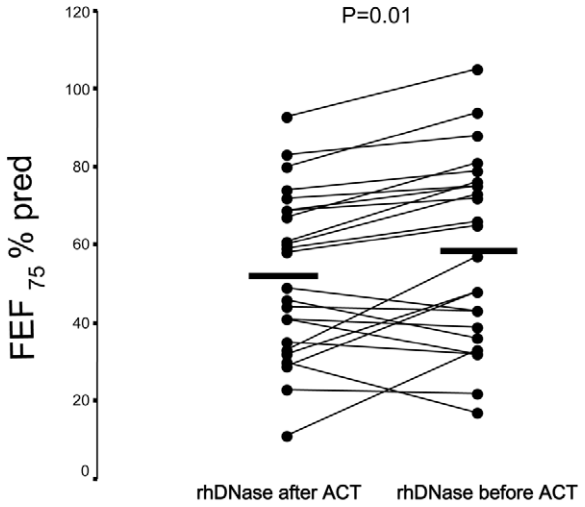

Fig. 1. FEF_{75} % predicted when dornase alfa was inhaled 30 minutes after versus immediately before ACT: results after 3 weeks' treatment. Lines connect individual data points. Bars represent mean values [8]. Reprinted with permission of John Wiley & Sons, Inc..

Table 2
Mean lung function (% predicted) with range after two and three weeks of dornase alfa treatment before or after ACT [8]. Reproduced with permission of John Wiley & Sons, Inc.

	FVC %	FEV_1 %	FEF_{75} %
After 2 weeks			
RhDNase after ACT	94.8 (76–131)	89.5 (68–116)	54.2 (18–104)
RhDNase before ACT	92.5 (72–123)	87.1 (57–107)	54.1 (8–103)
p-value	0.12	0.18	0.98
After 3 weeks			
RhDNase after ACT	94.1 (75–131)	88.3 (67–105)	52.5 (11–93)
RhDNase before ACT	93.3 (75–127)	89.4 (66–113)	58.3 (17–105)
p-value	0.65	0.58	0.01 ‡

‡ $p < 0.05$.

B: Dornase alfa before versus after sleep

Again, 25 patients were enrolled and 24 completed the study. Mean age was 13 years and, while FVC was normal,

Table 3
Characteristics of the population in the study of dornase alfa before versus after sleep at baseline for groups I and II (numbers of patients, or mean with SD) [9]. Reproduced with permission

	Group I	Group II	
N	11	13	NS
Sex (male/female)	3/8	5/8	NS
Age (years)	12.5 (4.5)	13.5 (3.4)	NS
FVC (% predicted)	81 (9)	82 (22)	NS
FEV_1 (% predicted)	74 (12)	76 (27)	NS
FEF_{75} (% predicted)	49 (32)	49 (34)	NS
Use of TOBI (*n*)	3	5	NS

mean FEV_1 was slightly and FEF_{75} considerably below normal limits at baseline. The treatment groups were well matched (Table 3). There was no significant difference between groups in any of the efficacy or safety parameters after either 1 or 2 weeks.

4. Discussion

In patients with well preserved lung function, the most prominent response to dornase alfa is in the peripheral airways [6]. Therefore spirometric measures of peripheral airflow such as FEF_{75} are more sensitive endpoints than FEV_1 for comparing dornase alfa regimens with respect to ACT in this population.

Although it is accepted that maximal spirometric responses to dornase alfa are achieved after 2 weeks of treatment, long-term studies suggest that they reach a peak at 1–2 weeks [5] or 4–12 weeks [6] of treatment but shorter time intervals have not been studied. The optimum duration of therapy for determining maximum short-term responses is therefore not clear. The result of the study of Fitzgerald et al. [7] is consistent with our results in that no significant difference was detected after two weeks of treatment. While 2 weeks may be too short to detect the maximal response to treatment, an alternative explanation for their result is that variability among patient responses to the initiation of drug treatment may have been greater than the variability between dornase alfa regimens, making it difficult to detect small differences between regimens. Furthermore, the extent of inhaled antibiotic use in their subpopulations with and without chronic colonisation by *Ps. aeruginosa* was not described. If, as suggested [10], dornase alfa improves penetration of inhaled antibiotics into sputum and biofilms, then uncontrolled differences in the use of such antibiotics may have confounded the trial results.

A more recent randomised crossover study has reported that FEF_{75} increased by 20% and quality of life was significantly improved when patients' regimens were modified for 2 weeks to allow dornase alfa to dwell in the airways for >6 hours as opposed to <6 hours before their usual ACT session [11]. The actual median dwell times were 15 minutes versus 11.1 hours. Unfortunately, the shorter dwell time of 15 minutes is insufficient to permit the full effect of dornase alfa on sputum *in vitro* [3] but the long dwell time is probably responsible for the great difference in FEF_{75} between the two regimens. Our study indicates that a dwell time of 30 minutes before ACT is already more effective than administering dornase alfa immediately after ACT, and suggests that 30 minutes may be the minimum dwell time for optimal efficacy. In other respects, the results of Wilson et al. are consistent with our own.

Our study of dornase alfa inhaled before versus after sleep, with ACT performed in the morning, is reassuring. There was no sign of decreased tolerance to dornase alfa during sleep, despite the facts that, during sleep, mucociliary clearance [12,13] and the cough reflex [14] are depressed and a quiet tidal volume pattern of breathing supervenes [15,16]. Specifically, oxygen saturation was not reduced during the night and there was no increased cough. Therefore, in patients with mild to moderate CF lung disease who perform ACT in the morning, our data indicate that it is equally safe and effective to administer dornase alfa before sleep and upon awakening. This implies that the actual timing of dornase alfa administration during the day is not critical, and that patients may therefore choose the most convenient time to inhale it.

The endpoint of our study on timing with respect to sleep was assessed after 2 weeks' treatment with dornase alfa, while a significant difference in peripheral flow was detected after 3 but not 2 weeks' treatment in our study with respect to ACT. Nevertheless, Wilson [11] found a significant difference between short and long dwell times already after 2 weeks. While further research may explain this discrepancy, we believe that future studies should extend the duration of therapy to at least 3 weeks.

In more severe lung disease, peripheral flows may well have deteriorated irreversibly and FEV_1 may be a more appropriate endpoint than FEF_{75} for discriminating between drug regimens [17]. The optimal timing of dornase alfa with respect to ACT and the safety of an overnight dwell need further research in such patients.

Finally, delivery to the lungs of any inhaled medication is generally inefficient and depends on the aerosol device employed [18]. New devices that generate smaller particles with a limited size range may be more effective in delivering aerosol to the peripheral lung, and may have an important impact on the effectiveness of dornase alfa [18].

5. Conclusions

In mild or moderate CF lung disease, it is reasonable to conclude that it is more effective to administer dornase alfa 30 minutes before ACT than shortly after ACT. In addition we showed that inhalation of dornase alfa immediately before sleep is as safe and effective as its administration in the morning. This is consistent with the hypothesis that the major role of dornase alfa is to facilitate expectoration of sputum during ACT. Patients may choose the most convenient time of day for its inhalation. The optimal regimen for patients with advanced lung disease requires further study. New inhalation devices may enhance the efficacy of dornase alfa by improving its deposition in the peripheral lung.

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Conflict of interest statement

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